News & Views

Research Highlights

Highlights from the latest articles in cardiology

Drospirenone and its linkage to venous thrombosis: can large registry data tell us anything definitive?

Robert J MacFadyen

University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Dudley Road, Birmingham, B23 7QH, UK
robert.macfadyen@swbh.nhs.uk

Evaluation of: Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using combined oral contraceptives containing levonorgestrel: case–control study using United States claims data. *BMJ* 342, d2151 (2011).

Controlling population growth is a priority for survival of the planet. We are currently not succeeding in that goal and new tools are needed. Predominantly, female fertility control has been the easiest therapeutic target and a variety of contraceptive strategies exist with few fundamental developments in approach in recent decades. This article (one of two from the same UK-based epidemiology group) is of interest as it explores the relationship between a new variant of progestogen-based contraception. It uses a long-established community care database known as the UK General Practitioner Research Database. Unfortunately, this paper also serves almost as a model of the significant weaknesses of clinical research by statistical association, particularly in addressing the safety of a drug treatment given in poorly defined patient exposures, indications and outcomes.

The goal is highly commendable: to explore the well-known linkage to thrombosis inherent in hormone-based contraception (both estrogen- and/or progestogen-based, dependent on dose; duration and exposure time) with a new chemical moiety. However, this aim is limited by the poor ability of database research to define and refine, with reasonable certainty, critical confounding cofactors in population linkage and it would appear here to also confirm the critical clinical end points. Ultimately, the attraction for researchers of the raw and ill-refined statistical 'power of numbers', inherent in large long-established registries, appears to overwhelm the importance of accurately addressing the research question. Thus, a generic research group with no specialist program is attracted to an area and applies the statistical power of the database to address an area that, in clinical terms, they have little or no personal research experience within. Numbers appear to blind many research groups to the error of population association by statistics alone. These two particular reports have attracted criticism in this regard, although others with an opposing view point have also used their publications to justify their own diametrically opposite opinions. This says more about the limitations of the technique than anything bad about the aims or motivation of the researchers and commentators.

On reflection, drospirenone, a spironolactone analog with progestogen properties, is a credible and effective contraceptive preparation, but the evidence that it could be a major step forward in population control in terms of its safety profile is hard to deduce from heavily confounded and largely unconfirmed database work such as this. That an association exists between drospirenone use and thrombosis in this analysis seems clear but whether it is valid and independent is debatable and most certainly not proven. The key to all research is the quality of verification, down to someone taking the care to verify individual patient event data. This has analogy to the clinical events monitoring of any multinational controlled clinical trial. This is hugely expensive in time and money.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

There is no substitute for that effort and investment in quality. The lack of such effort in many database association studies and the impact this has on the strength of any relevant conclusions that may be drawn, remain profound. Postmarketing surveillance of drug therapies is a complex area but one in which high-quality verified data on individualized clinical events is the key to verification of safety and or efficacy. There is no escaping the impact of dose response; duration and individualized patient susceptibility to key adverse events (e.g., in this instance to exclude individualized pre-exposure thrombotic risk assessment, dose and duration of exposure where the treatment is profoundly more likely to induce thrombosis soon after exposure and not after many years of use, age and smoking). The bias of individual prescribers in patient selection is not addressed and thus, case–control matching is largely invalid. For the present, drospirenone is legitimately regarded as a safe and effective contraceptive agent alone or in combination and has appropriate postmarketing data to continue to be used as such for such a major global problem as fertility control. Its claims for added safety in certain settings remain possible but not proven. Suggestions of significant added harm appear unjustified from this type of data and analysis.

The STICH trial and coronary revascularization: the impact of crossover on interpreting a complex clinical trial involving standard coronary surgery

Evaluation of: Velazquez EJ, Lee KL, Deja MA *et al.* Coronary artery bypass surgery in patients with left ventricular dysfunction. *N. Engl. J. Med.* 364(17), 1607–1616 (2011);
Bonow RO, Maurer G, Lee KL *et al.* Myocardial viability and survival in ischaemic left ventricular dysfunction. *N. Engl. J. Med.* 364, 1617–1625 (2011).

Significant contemporary outcome trials addressing the application of coronary revascularisation by surgery are rare. The standard of care set by this modality and reasons to question its effectiveness in symptom relief for the majority and in improving prognosis and survival for a small proportion of treated patients are limited. However, the application and net added value of revascularisation surgery in patients with impaired ventricular function (i.e., damaged heart muscle systolic contraction) is less clear. One more subtle aspect of surgical revascularisation strategies that has received attention in this programme is the principle of using non-invasive triage to define the viability of myocardium in patients with epicardial coronary disease and potential scar prior to coronary surgery. The primary hypothesis tested in STICH was that coronary surgery added significant benefit in patients with ischemic cardiomyopathy compared with best medical therapy (the so called 'hypothesis 1'). The added concern was that exposing patients to operative risk for unclear benefit could be presumed in patients whose myocardium is already dead or at the least scarred (hypothesis 2). This presumption was further tested looking at the value of using noninvasive means to confirm viable ischemic myocardium was present before any surgery was completed and the potential impact of no surgery in those with no reversibility. A landmark trial, it is widely regarded as likely to be the last major such effort for a considerable period.

Over a median 56 months of follow-up in ischemic cardiomyopathy patients (all LVEF < 35%) 41% of patients (n = 602) on best medical therapy died compared with 36% of the CABG group (n = 610) on an intention to treat analysis. This analysis did not suggest that a statistically significant mortality benefit existed with surgical treatment. However with an eventual 17% crossover of medical patients to CABG (that had been anticipated during power calculation, up to 20% crossover) there was considerable scope for dilution bias via this route. While the main headline result showed no statistical benefit, it was clear that CABG was more effective in reducing cardiovascular events after baseline risk factors were compared and also where composite secondary end points were considered. Moreover, in those who were not crossed over (an 'as treated' analysis), a total of 537 patients in medical therapy and 555 patients in CABG, there was a statistical benefit for surgery (hazard ratio: 0.76 $p < 0.005$). In addition, there was benefit at 1 year notwithstanding an expected early mortality due to immediate surgical complications. Therefore, it remains interesting that after all these statistically positive outcomes, a lot was made of the lack of expected benefit and that surgery was "not superior to optimal medical therapy", a view that while technically correct for the intention to treat analysis, seems to be a woefully inadequate and potentially misleading summary of a very complex and challenging trial. The difficulties in recruitment were at the heart of this result and its interpretation.

With respect to the secondary hypothesis, that testing of myocardium to ensure viability was residual prior to completing a revascularisation procedure, a further

interesting result was defined. In a companion report to the main trial it was concluded that this step did not impact upon the overall effectiveness of surgery. Thus, there was a failure of ischemic viability testing to substratify patients who may or may not benefit. The interpretation of this result has also shown quite a bit of variance. Many feel that this investigational step has been shown by STICH hypothesis 2 to be portrayed as ineffective in triaging those who will benefit. However, this could also be interpreted that viability testing prior to CABG in ischemic cardiomyopathy should not be used to preclude surgery in those who remain symptomatic despite maximal medical therapy and have residual obstructive coronary disease. Thus, the absence of reversibility need not be interpreted as, strictly speaking, a reason not to do revascularisation surgery. Further subanalysis of this huge trial effort (the numbers are rather modest for a contemporary cardiovascular trial), which took many more years to recruit than planned, are underway and will undoubtedly reveal many new insights. The reason that this trial took so long is that it challenged standard practice and thinking where presumption of the benefit of surgery over medical therapy is widespread. Patients who could benefit from surgery, in the understanding of their physicians and surgeons, were frequently not recruited to this randomized trial for fear of them being disadvantaged by that process. The large crossover to surgery confirmed that practice and has clearly compromised the standard intention to treat analysis. It does not mean the trial was not very worthwhile nor that it is uninterpretable but does mean that the attention to detail of individual outcomes and management will continue to reveal new information for some years to come.

The emergence of excellence in adjunctive antiplatelet therapy: ticagrelor versus clopidogrel in acute coronary syndrome management

Evaluation of: Wallentin L, Becker RC, Budaj A *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* 361, 1045–1057 (2009); Wallentin L, Becker RC, James SK, Harrington RA. The PLATO trial reveals further opportunities to improve outcomes in patents with acute coronary syndromes. *Thromb. Haemost.* 105(5), 760–762 (2011).

The continuing analysis and debate over the PLATO trial of ticagrelor compared with clopidogrel in combination with aspirin continues to present a landmark cardiovascular study. For the first time a study in adjuvant pharmacotherapy accompanying a coronary stenting (present in the vast majority of cases in this huge study of 18,624 subjects) has revealed a reduction in all cause mortality as well as the specific cardiovascular end point of death from myocardial infarction; stroke or cardiovascular death from 11.7% with clopidogrel to 9.8% with ticagrelor. This was achieved in a predominantly eastern European-based study of both non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) at acute presentations of obstructive coronary disease.

The majority of patients in the PLATO trial were treated by direct coronary intervention and the outcome favored ticagrelor overwhelmingly in every respect but, most notably, in postprocedural bleeding, an as yet poorly understood aspect linked to adverse outcome (not all of which is explained by fatal bleeding or exposure of underlying malignancy). The overall mortality rate has attracted some comment as this was higher than some comparable large outcome trials of the combination of clopidogrel and aspirin (CURE-PCI; CREDO) in acute patients or more stable patients managed with or without mechanical coronary intervention (ACUITY; CURE; CHARISMA) or in patients with NSTEMI. Most reasonable subgroup analysis from the trial contained a similar end result favoring ticagrelor (e.g., regardless of age, race, gender, STEMI/NSTEMI, stent or nonstent care).

The evident lack of benefit with ticagrelor in the geographical subgroup of subjects recruited in North America has possibly attracted undue attention due to the size and importance of this commercial market. A variety of reasonable explanations have been proposed relating to aspirin dose (e.g., generally higher in North America than in the rest of the world). However, the main issue in its interpretation was the very small contribution from this region only 1814 patients from the total trial of 1714 from Asia/Australasia, 1237 from Central/South America and 13,598 in Europe/Middle East/Africa, makes such segregation illogical and invalid. While the geographical subanalysis is intriguing it is misleading due to its lack of statistical power to separate any potential difference between the agents.

Another intriguing observation through the 9 months of trial follow up currently published is the suggestion of a progressive reduction in mortality outside the reduction in reinfarction rates (divergent Kalpan–Meier curves again favoring ticagrelor). This might plausibly relate to the small reduction in major bleeding events but as in many other trials of this sort the exact etiology of bleeding to mortality is not yet clear and is not simply explained by fatal major bleeding *per se*. More detailed analysis of this further aspect of this trial is awaited as this was not expected and most previous comparative trials produce a predictable parallel outcome effect.

The net mortality benefit on such short-term follow-up, however impressive, remains rather small and much debate has appeared on the cost–effectiveness of the intervention. In practical terms the impact of this result is great but taking advantage of this result by substituting this drug for alternatives is challenging for many health economies. Unlike the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI 38) outlining the primary efficacy of prasugrel in a comparable setting (the recent main competitor in the combination antiplatelet market to clopidogrel) we have as yet no subanalysis suggesting any group of high-risk patients who might particularly benefit from this additional cost. TRITON has been widely used to justify the selective use of prasugrel in diabetic patients, with drug eluting stent technologies and in STEMI only (a much less prevalent acute presentation than NSTEMI). Thus, the sheer size of PLATO, while in some ways has underlined the clear advantage of ticagrelor above clopidogrel, has not given any guide as yet to the cost-effective application of such a combination. As an indication the annualized cost of generic clopidogrel is £30.75 and that of prasugrel is £630.17 and ticagrelor is £713.70 with an additional cost per QUALY ranging from £3966 to £8905.

Bivalirudin: an old drug shows itself useful in combination with unfractionated heparin

Evaluation of: Koutouzis M, Lagerqvist B, James S *et al.* Unfractionated heparin administration in patients treated with bivalirudin during primary percutaneous coronary intervention is associated with lower mortality and target lesion thrombosis: a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Heart* doi: 10.1136/hrt.2011.224709 (2011) (Epub ahead of print).

The Scandinavian Coronary Angiography and Angioplasty Regisitry (SCAAR) group reports from a large percutaneous coronary angioplasty registry data analyzed for the impact and effectiveness of bivalirudin on bleeding rates during these procedures. Bivalirudin is a remarkable direct thrombin inhibitor, which is useful for intravenous dosing, that has been available for many years. It has increasingly developed a niche and evidence base in its application during coronary intervention and potentially supplanting both alternative anti-thrombotic drugs used in isolation such as unfractionated heparin, low-molecular-weight heparin and fondaparinux combined with platelet antagonists. The rationale for this is that bivalirudin has a dose dependent potential to also inhibit platelet activity and thus challenge the use of adjuvant glycoprotein IIb/IIIa inhibitors during stent implant and other procedures. Concurrently there was some concern about the key dosing strategies appropriate for each activity are correctly combined in use during percutaneous coronary intervention (PCI) to maximize stent patency (minimizing stent-related thrombosis) but also to minimize postprocedural bleeding rates associated with mortality. It appeared that combined use of unfractionated heparin and bivalirudin was key to a successful balance.

Earlier open label studies give one level of evidence and the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) study program suggested bivalirudin did perform better in the context of acute coronary occlusion associated with STEMI with respect to postprocedural bleeding. Sadly, there was a suggestion of slightly more stent thrombosis in this critical application. The key to this result was undoubtedly the dosing of bivalirudin and possibly also in the addition of unfractionated heparin to some (but not all) patients during the procedure. The SCAAR group therefore sought to explore further the importance of supplementing the anti thrombin effect on bivalirudin and heparin bolus during PCI, but this time focused more clearly on STEMI. They selected

the first PCI in patients receiving bivalirudin plus unfractionated heparin only (dose not recorded). The weaknesses of registry data alluded to previously were much less prevalent here as detailed individual case information was defined both in terms of burden of disease; procedure and key complications.

The end points of target lesion thrombosis and bleeding events were collated in 1928 patients on bivalirudin and 1068 patients on bivalirudin plus unfractionated heparin. The raw impact on death or target lesion thrombosis was clear and showed an obvious advantage for the combination of unfractionated heparin and bivalirudin above bivalirudin alone, which was nicely sustained out to 1 year and showed a parallel curve with no late loss of effectiveness. Critically, there was no increase in major bleeding despite this increased efficacy in preventing thrombosis in newly deployed stents. The two patient registry groups were very broadly comparable although, interestingly, those with bivalirudin and heparin therapy in fact had a slight and significant increase in drug eluting stent deployment (associated with more late in stent thrombosis). Most were pretreated with a thiopyridinedione antiplatelet combination drug such as clopidogrel, but did not receive further adjuvant antiplatelet therapy (other than bivalirudin) in the catheterization laboratory. This pattern is associated with a major overall procedural cost reduction. The outcomes are very intriguing that this old drug has in fact shown itself to be a very useful adjunct to unfractionated heparin alone and might offset a large part of procedural costs attributable to acute use of glycoprotein IIa IIIb inhibitor use. Randomized comparisons are clearly still pertinent but here is an 'old dog' that really can be said to have a new life in this routine interventional application in cardiology.